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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
09/462,740	04/05/00	MURAKAMI	H	Q57531

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EXAMINER	
PARAS JR,P	
ART UNIT	**PAPER NUMBER**
1632	6

DATE MAILED: 07/24/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application N .	Applicant(s)	
	09/462,740	MURAKAMI ET AL.	
	Examiner	Art Unit	
	Peter Paras, Jr.	1632	

-- The MAILING DATE f this communication appears on the cover sheet with th correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-7 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-7 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☒ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☒ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15)☒ Notice of References Cited (PTO-892)

16)☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .

18)☐ Interview Summary (PTO-413) Paper No(s). _____ .

19)☐ Notice of Informal Patent Application (PTO-152)

20)☐ Other: .

DETAILED ACTION

Claim Objections

Claim 1 is objected to because of the following informalities: the phrase "other than man" should be written as "non-human". Appropriate correction is required.

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> **The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.**

Claims 1-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-7 are indefinite because the invention is claimed in the plural (for example, transgenic mammals). Appropriate correction is required.

Claims 4-5 use language which is unclear. The term "promoter gene" as written is indefinite. A promoter is a nucleic acid sequence or region which does not encode an expression product. A gene is a nucleic acid sequence which encodes an expression product. It is recommended to delete the term "gene" which directly follows the term "promoter".

Claim 4 is unclear as written. The phrase "carry promoter gene of the porcine complement inhibitor (pMCP) at an upstream locus of the human complement inhibitor

(DAF/CD55) gene" is indefinite. It is indefinite because the function of pMCP promoter is not clear. Is the pMCP promoter operably linked to the DAF/CD55 gene such that it directs expression of DAF? The claim should be rewritten to clearly define the relationship of the pMCP promoter and DAF. Also the article "a" should be inserted between the terms "carry" and "promoter".

Claim 5 uses language which is unclear. The phrase "or its parts" does not convey any clear meaning since the nucleotide sequences of the "parts" have not been disclosed. Can all parts of Sequence 1 function as a promoter? Are all the "parts" of sequence 1 which are claimed defined by specific sequence identification numbers?

Claims 1 and 4 use indefinite language. For example, the terms "carrying" and "carry" do not convey a clear meaning. It is not clear how carrying a transgene correlates to integration in the host genome. It is suggested that the terms "comprise" and "comprising" be used in place of "carry" and "carrying" respectively. Claims 2-3, and 5-6 depend from claims 1 and 4 and are rejected accordingly.

Claim Rejections - 35 USC § 112, 1st paragraph

Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 1 is directed to transgenic mammals comprising human DAF/CD55 wherein hDAF is expressed in same mammals organs and tissues. Claims 2-3 are directed to the same transgenic mammals wherein expression of DAF/CD55 is in endothelial cells. Claims 4-5 are directed to the same transgenic mammals wherein the DAF/CD55 gene is operably linked to the porcine complement inhibitor (pMCP) promoter, whose nucleotide sequence is defined in sequence 1. Claims 6-7 are directed to the same transgenic mammals, in particular pigs or mice.

The specification teaches the creation and identification of transgenic mice and pigs both of which comprise the human DAF/CD55 gene operably linked to the pMCP promoter. DAF/CD55 appears to be functionally expressed in same transgenic pigs and mice. The specification suggests that organs from transgenic mammals, particularly pigs and mice, which comprise functional human DAF can inhibit the complement cascade in a recipient and therefore prevent and/or suppress hyperacute rejection of transplanted organs. The specification however, fails to teach any successful transplantation of organs from transgenic mammals comprising human DAF/CD55. The specification fails to show suppression of hyperacute rejection in a recipient of an organ from a transgenic mammal comprising human DAF/CD55. Thus, as enablement requires the specification to teach how to make and **use** the claimed invention, the specification fails to enable the use of any tissue or organ from a transgenic mammal comprising human DAF/CD55 for xenotransplantation.

[**Note** that although the claimed transgenic mammals are not limited to expression of the transgene at a level resulting in prevention of hyperacute rejection

(resulting from activation of the complement cascade) of transplanted organs, with regard to claim breadth, the standard under 35 U.S.C. §112, first paragraph, entails the determination of what the claims recite and what the claims mean as a whole. In addition, when analyzing the enabled scope of the claims, the teachings of the specification are to be taken into account because the claims are to be given their broadest reasonable interpretation that is consistent with the specification. As such, the broadest reasonable interpretation of the claimed transgenic mammals having cells which harbor a human DAF/CD55 gene is one that expresses the transgene at a level sufficient to result in prevention of hyperacute rejection of xenotransplanted organs from same transgenic mammalian donors *(i.e.*, it is unknown what other purpose these transgenic mammals would serve if the human DAF/CD55 transgene is not expressed at a sufficient level to or requires other factors to prevent hyperacute rejection of xenotransplanted tissues or organs in a recipient, thus allowing these transgenic mammals to function as organ donors).]

While the specification teaches transgenic mammals, particularly pigs and mice, comprising human DAF/CD55, the specification however, fails to provide any relevant teachings or guidance with regard to transplantation of organs or tissues from human DAF/CD55 mammals. One of skill would **not** be able to rely on the state of the xenotransplantation art for an attempt to successfully transplant organs from the same mammals into a recipient. This is because the state of the art of xenotransplantation is not a predictable art with respect to suppression of hyperacute rejection in organ transplant recipients. While the state of the art of transgenics is such that one of skill in

the art would be able to produce transgenic animals comprising a transgene of interest, in particular human DAF/CD55; it is not predictable if human DAF/CD55 would be expressed at a level and specificity sufficient to allow xenotransplantation of transgenic organs by preventing hyperacute rejection. Furthermore, it is not predictable if expression of DAF/CD55 (in a transgenic organ) **alone** is enough to suppress the complement cascade and prevent hyperacute rejection in a recipient. Kuipers et al (1997, Transgenic Research, 6: 253-259) support this observation by reporting that to enable the use of hDAF transgenic pigs for the purpose of clinical organ transplantation it is extremely important that high expression of the hDAF transgene is confirmed at critical sites in the organ such as the endothelium (page 257 column 2 paragraph 2 lines 1-3). The expression of the genetic construct is critically dependent on the site of integration and the promoter sequence used report Artrip et al (1997, Cur. Opin. Cardiol., 12: 172-178). Artip et al further report that transplantation of transgenic cardiac grafts expressing hDAF/CD55 into nonimmunosuppressed monkeys survived a median of 5.1 days; also transplantation of transgenic cardiac grafts expressing hDAF/CD55 and CD59 survived only 30 hours in splenectomized and immunosuppressed baboon recipients (page 176 column 1 paragraph 2). The resistance to hyperacute rejection was dependent on translocation of the human complement regulatory proteins (CRPs), DAF/CD55 for example, to endothelial cells and was **short-lived** following xenotransplantation. The example (10) provided by the specification shows that DAF/CD55 operably linked to the pMCP promoter is biologically active in transgenic pigs and mice by demonstrating that erythrocytes from both

transgenic animals are resistant to lysis in the presence of human serum for 1.5 hrs in an ***in vitro*** assay. Table 1 (page 18) in the specification compares the tissue distribution of DAF expression under control of hMCP and pMCP promoters in transgenic mice. The pMCP promoter directs a higher DAF level of expression in endothelial tissue of most organs (according to Table 1) in a transgenic mouse. The specification, however, fails to correlate detection pMCP-DAF/CD55 expression in endothelial tissue of transgenic pigs and mice with suppression of hyperacute rejection in a transplantation recipient of a DAF/CD55 transgenic organ, providing only the above mentioned ***in vitro*** assay. The specification does not provide any **in vivo** working examples or guidance which can correlate DAF/CD55 expression with suppression of hyperacute rejection in a transplantation recipient of a DAF/CD55 organ. The obvious differences between **in vitro** and **in vivo** assays make it virtually impossible to predict results based solely on **in vitro** experimentation with respect to hyperacute rejection and xenotransplantation.

Note, if a nexus can be made which can correlate expression of DAF/CD55 under the control of the pMCP promoter with **in vivo** suppression of hyperacute rejection and xenotransplantation in transgenic pigs and transgenic mice, the scope of the invention will be enabled only for those transgenic pigs and transgenic mice.

Therefore, in view of the quantity of experimentation necessary to determine the parameters listed above for the production of transgenic DAF/CD55 mammals whose organs can resist hyperacute rejection, the lack of direction or guidance provided by the specification for the production of any transgenic DAF/CD55 mammal whose organs

can resist hyperacute rejection in a recipient, the absence of working examples for the demonstration or correlation of expression of DAF/CD55 in a transgenic mammal with **in vivo** suppression of hyperacute rejection of a DAF/CD55 transgenic organ in a transplantation recipient , in particular when the transgene comprises DAF/CD55 coding sequences under the control of any and all promoters, and more particularly when the expression of the transgene must occur at a level resulting in suppression of hyperacute rejection, and the unpredictable and undeveloped state of the art pertaining to suppression of hyperacute rejection and xenotransplantation, it would have required undue experimentation for one skilled in the art to make and/or **use** the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> **A person shall be entitled to a patent unless –**
>
> **(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.**

Claims 1-3 and 6-7 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Rosengard et al (1995, Transplantation, 59(9): 1325-1333).

Claim 1 is directed to transgenic mammals comprising human DAF/CD55 wherein hDAF is expressed in same mammals organs and tissues. Claims 2-3 are directed to the same transgenic mammals wherein expression of DAF/CD55 is in endothelial cells. Claims 6-7 are directed to the same transgenic mammals, in particular pigs or mice. For the purposes of prior art rejections the claims are interpreted to being

drawn only to the product, transgenic mammals comprising DAF/CD55, and not the intended use of the product.

Rosengard et al teach a transgenic pig which comprises human DAF/CD55 (page 1325 column 2 paragraph 2). Patterns of hDAF/CD55 show widespread endothelial cell distribution (page 1326 RESULTS paragraph 2). Expression of hDAF/CD55 was detected in the endothelial cells of the kidney, liver, heart, lung, and aorta (page 1327 paragraph bridging columns 1-2). Thus, the teachings of Rosengard et al meet all of the instant claim limitations.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> **(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.**

Claims 1, 4-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rosengard et al (1995, Transplantation, 59(9): 1325-1333) in view of Toyomura et al (1 Jan 1997, WO 9700951).

Claim 1 is directed to transgenic mammals comprising human DAF/CD55 wherein hDAF is expressed in same mammals organs and tissues. Claims 4-5 are directed to the same transgenic mammals wherein the DAF/CD55 gene is operably linked to the porcine complement inhibitor (pMCP) promoter, whose nucleotide

sequence is defined in sequence 1. For the purposes of prior art rejections the claims are interpreted to being drawn only to the product, transgenic mammals comprising DAF/CD55, and not the intended use of the product.

Rosengard et al teach a transgenic pig which comprises human DAF/CD55 (page 1325 column 2 paragraph 2). Patterns of hDAF/CD55 show widespread endothelial cell distribution (page 1326 RESULTS paragraph 2). Expression of hDAF/CD55 was detected in the endothelial cells of the kidney, liver, heart, lung, and aorta (page 1327 paragraph bridging columns 1-2).

Rosengard differs from the claimed invention regarding the use of the pMCP promoter to direct expression of the DAF/CD55 transgene.

Toyomura et al teach the cloning and sequencing of a porcine complementary inhibitor cDNA (pMCP) from porcine vascular endothelium. Toyomura et al also suggest that the promoter of pMCP can be obtained using pMCP cDNA. Toyomura et al suggest that the pMCP promoter may be useful for the expression of human complement inhibitor in porcine to reduce rejection observed in the porcine-to-human organ transplantation (please see abstract provided).

Accordingly, in view of the teachings of Toyomura et al., it would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made, to modify the transgenic construct of Rosengard by use the pMCP promoter to direct expression of hDAF/CD55 in transgenic mammals with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make such a modification as it was an art-recognized goal to achieve high levels of

expression of human complement regulatory proteins, including DAF/CD55, in endothelial cells and particularly since Toyomura et al. suggest that the pCMP promoter can be useful in directing expression of human complement inhibitor to the endothelial cells of porcine for study of rejection of organs in porcine-to-human transplantation.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Peter Paras, Jr., whose telephone number is 703-308-8340. The examiner can normally be reached Monday-Friday from 8:30 to 4:30 (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasemine Chambers, can be reached at 703-308-2035. The FAX phone number for art unit 1632 is 703-308-0294.

Inquiries of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is 703-308-0196.

Peter Paras, Jr.

Art Unit 1632

Patent Examiner
1632